REMARKS/ARGUMENTS

After entry of the amendment, claims 62-66, 70-73, 75-90, 98-100, 102-127 and 131-133 remain pending. Claims 62-63, 90, 126-127 and 131-133 have been amended. Claim 67 has been cancelled.

In response to the Examiner's comments, Applicants have amended the claims to limit the scope of transgenic animals to mammals. Also in response to the Examiner's comments, Applicants have amended the claims to confirm that the surrogate mother is a "suitable host, " in other words, that it is able to carry the embryo to maturity or term. Applicants have also clarified that the oocyte, two cell embryo or zygote is capable of producing a viable nuclear transfer unit. This amendment addresses the Examiner's concerns about the cell cycle of the recipient, as it requires that the oocyte, two cell embryo or zygote be capable of receiving the donor genetic material and creating a viable nuclear transfer unit. Applicants have also amended the claims to recite "cattle," instead of cow and bull. Support is found on page 8, Paragraph 0138, of the published specification.

As discussed in previous communications, this application describes and claims a method to produce a genetically modified mammal by genetic modifying a somatic cell via gene targeting and then transferring the genetic material to a recipient cell to produce a nuclear transfer unit which can be used to produce a live animal. Specifically, claims are generally drawn to a method to produce a non-human transgenic mammal, involving modifying the nuclear genome of a somatic cell with a normal karyotype at an endogenous locus by a genetic targeting event; transferring the modified nuclear genome of the somatic cell to an oocyte, two cell embryo or zygote which is capable of producing a viable nuclear transfer unit; activating the nuclear transfer unit thereby producing an embryo, transferring the embryo to a surrogate mother which is a suitable host, and allowing the embryo to develop, inter alia, to term.

Claim Rejections - 35 U.S.C § 112

In the Office Action mailed on October 21, 2005, the Examiner rejected claims 62-66, 70-73, 75-90, 98-127 and 131-133 under 35 USC § 112, first paragraph as failing to comply with the enablement requirement. Applicant responds to this rejection below.

(i) Somatic Donor Cells

The Examiner uses several publications to attempt to establish that not all somatic cells can be used for nuclear transfer and that as of the priority date, nuclear transfer technology was unpredictable with regard to what cell types to use as donors. These publications, discussed below, are Oback and Wells, Campbell, Tian, Li and McEvoy.

Oback and Wells

The Examiner again cites Oback and Wells for the proposition that it was unpredictable in 1999 which somatic cells could have been used to donate genetic material to a recipient cell to create a successful nuclear transfer unit. Applicants respond that it was not considered unpredictable which mammalian somatic cells could be used to donate genetic material, as any somatic cell could be used, as further discussed below and in the declarations of Dr. Ayares and Dr. Piedrahita The Examiner seems to heavily focus on the concept of cloning efficiency in her remarks. With respect, Applicants point out that cloning efficiency is different from clonability. There is no requirement under the U.S. patent laws that a technique be highly efficient or work perfectly to be part of a patentable process. See *Radio Corporation of America v. E.J. Edmond & Co.*, 20 F.2d 929 (S.D. N.Y. 1927); *Hanson v. Alpine Valley Ski Area, Inc.*, 204 U.S.P.Q. (BNA) 794, 1977 WL 22812 (E.D. Mich. 1977), *aff'd*, 611 F.2d 156 (6th Cir. 1979).

The Examiner again refers to Table 1 of Oback and Wells, which reports cloning efficiencies of a number of donor somatic cells. In Applicants' response dated July 25, 2005, Applicants provided a Declaration of David Ayares which established that there is no fundamental reason why any somatic cell with a normal karoytype cannot act as a nuclear donor, and that the issue of cloning efficiency is simply one of numbers-some somatic cells are more efficient than others for reasons described in the literature at the time and discussed by the Examiner in her action. The response to a low efficiency donor cell is simply to conduct more of the same embryo transfers until viability is achieved. According to Paragraph 11 of the Ayares Declaration, repeating the experiment enough times to achieve success does not require a special or extra technique, it simply requires that one carry out the experiment more times. The fact that a repetitive laboratory work is required is not in itself indicia of undue experimentation. As stated by the Federal Circuit in *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996), the test for undue experimentation is "not merely quantitative, as a considerable amount of experimentation is permissible if it is merely routine." "The mere fact that repetitive

experimentation is required does not make it excessive where such experimentation is routine." *Discovision Associates v. Disc Manufacturing, Inc.*, 25 F.Supp.2d 301 (D. Delaware 1998); *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998), discussed further below (holding that a method for producing monoclonal antibodies was enabled where success with the technique commonly required repetition, noting that the lack of certainty was not attributable to a failure of disclosure in the patent specification).

The Examiner rejected Ayares declaratory statements on the basis that he relied on articles that established a positive cloning efficiency for certain cells for which Oback and Wells reported a 0% cloning efficiency which were published after the priority date of the patent application. A declaration presenting evidence of the state of the art at the priority date by a witness working in the field at the time must be considered and credited by the Examiner in the same manner as a publication as of that date. The post-priority date publications were merely corroborative support to the basic statement of Ayares that all somatic cells could have been used as nuclear donors as of the priority date. The basic evidence was the witness testimony from Ayares, not the post-priority date publications. Since Dr. Ayares is a named co-inventor of the present claims, Applicants now provide the Examiner with a declaration from a second scientist who was working in the field of nuclear transfer in 1999 who is not a named inventor and who has had no previous financial interaction with Revivicor, the owner of this application. The second declarant is Jorge A. Piedrahita, a Professor of Genomics in the College of Veterinary Medicine at North Carolina State University (NCSU). Dr. Piedrahita's research is focused on the production of transgenic animals by somatic cell nuclear transfer (SCNT) and on the development of methods of homologous recombination in somatic cells.

Dr. Piedrahita observes that independent researchers in the area of nuclear cloning in 1999 were highly skilled and highly educated. The scientists acting independently in these fields in 1999 had a Ph.D. degree and significant work experience in sophisticated laboratory molecular biology techniques. They were among the "elite" of the animal veterinary research profession. Dr. Piedrahita attests that it was understood and well accepted by him, and in his opinion by others, working independently in the field at the time that the genetic material from any somatic cell could be used in somatic cell nuclear transfer. It was also understood and discussed that the more differentiated the cell, the less efficient the reprogramming might be, however, that was expected and accounted for; in fact, the first cloned animal was produced using an adult, fully differentiated somatic cell as the nuclear donor (Dolly). It was generally

observed that some somatic cells had a higher cloning efficiency than others. However, Dr. Piedrahita, as well as others, distinguished cloning efficiency from cloning ability. Low cloning efficiency simply meant that more transfers were required to achieve a success. In 1999, Dr. Piedrahita knew of no somatic cell that for theoretical or technical reasons could not be used as a supply of genetic material for cloning, or in particular, mammalian cloning.

In 1999 and still today, Dr. Piedrahita was not aware of any publication reporting that a certain somatic cell could not be used for somatic cell nuclear transfer, and in particular mammalian cell SCNT. A number of articles discuss the efficiency of SCNT, but in 1999 and still today, to his knowledge, none have made a statement that SCNT cannot be successfully accomplished with any somatic cell using standard techniques in the industry. Dr. Piedrahita also notes that those in the field of SCNT live with low efficiency results and expect them in the area of nuclear transfer and cloning. These scientists are typically both time and resource constrained, and therefore use the somatic cells that are known to produce the highest numbers of live offspring simply out of convenience. That, however, should not and can not be interpreted as an implication that genetic material from other somatic cells can not be used.

Dr. Piedrahita comments that in his own work in 1999 and today, he typically uses fetal fibroblasts for SCNT. He has used other somatic cell types, such as follicular cells, but commonly uses fetal fibroblasts simply because they are easy to work with and the goal of his work is to efficiently produce live offspring. In 1999 and today, Dr. Piedrahita regularly transfers about 400 embryos to achieve a live birth via SCNT even with this highly efficient somatic cell. If in 1999 or today, Dr. Piedrahita were asked to carry out nuclear transfer to achieve a clone using a cell other than a fetal fibroblast, he would transfer far more, e.g., up to 2000 or more embryos, and would consider that a routine part of the lab work. If asked to clone a difficult or inefficient somatic cell, he would apply more resources and conduct more transfers as needed to achieve success. The transfer of a larger number of embryos naturally involves more work and cost, but can be carried out by repetition of standard techniques.

Dr. Piedrahita has read and he agrees with the Declaration of David Ayares. Dr. Piedrahita confirms that Dr. Ayares' Declaration represents the views of those working independently in the field of nuclear transfer in 1999. According to Dr. Piedrahita, there is no question that the concept of cloning efficiency is simply a reflection of the ratio of number of attempts and not any indication of the lack of clonability of the cell, and there is no good scientific rationale to support the position that any given somatic cell cannot be cloned.

Dr. Piedrahita specifically comments on the Oback and Wells paper. He spent six months as a Visiting Scientist/Fogarty Fellow in Hamilton, New Zealand in the laboratory of David Wells, the senior author on the Oback and Wells paper, to further his understanding and skill in SCNT. Oback worked in the same laboratory under the supervision of Wells. Dr. Piedrahita confirms that the Oback and Wells paper does not teach that there are somatic cells that are unclonable, and knowing Wells, he does not think that Wells would have made such a statement. The emphasis of the Oback and Wells paper is on cloning efficiency. Further, Dr. Piedrahita confirms that he, and he believes that others, and even Wells, would know that Table 1 of the paper describes populations of cell experiments that are too small to reach any definitive conclusion on an accurate cloning efficiency of the listed somatic cells. Oback and Wells focuses on differences among donor cells. The factors discussed in Oback and Wells are simply explanations, or rationalizations, of the differences in cloning efficiencies, not ultimate clonability.

Applicants have now provided the Examiner with two declarations from scientists working in the field at the relevant time. The Examiner is required to credit the testimony of declarants who provide statements about the state of the field and a technology as of the priority date based on personal knowledge in the same manner as publications. With regard to the details of carrying out the nuclear transfer process itself, the Examiner is directed to published information as of the priority date such as Coleman, Somatic Cell Nuclear Transfer in Mammals: Progress and Applications, Cloning, Vol 1, Number 4 1999/2000 and those references cited in paragraph 3 and 4 of the specification including WO 97/07668.

Campbell

The Examiner argues that the unpredictability of SCNT is further supported by the post-filing publication of Cambell et al. (Reprod. Dom. Anim., 40: 256-268 (2005)). In fact, Campbell begins his article with the positive statement that:

> It is now 8 years after the birth of Dolly, the first animal produced by nuclear transfer using a donor cell population established from an adult animal. During this time, the technique of nuclear transfer has been successfully applied to a range of mammalian species for the production of offspring using a plethora of donor cell types derived from both foetal and adult tissues. In addition, when coupled with genetic manipulation of the donor cells, transgenic offspring have been produced with a range of genetic modifications including gene knockouts and gene knockins.

He then states that, "Despite the apparent successes of the technology, the efficiency of development to live offspring has remained low and development abnormalities still occur."

It could not be more clear that Campbell, like Ayares and Piedrahita, acknowledges that SCNT works across a "plethora" of donor cell types, and that the Campbell article really addresses not whether SCNT is achievable with a range of donor cells, but instead attempts to increase the efficiency of the process. There is no statement in the Campbell article that any given somatic cell cannot be used for nuclear transfer nor that success cannot be accomplished.

Applicants also note that the Examiner referred to a quote from Campbell that "Unfortunately, no conclusion can be made on what is the most appropriate cell type for SCNT." There is no requirement under U.S. patent law that one claim or use only a "most appropriate" embodiment. Further, Campbell follows this statement with the observation that "However, what is certain is that cells derived from early embryos, fetuses, adult differentiated and post-mitotic cells have successfully been employed for the generation of cloned animals." (pg. 261, immediately following the quote provided by the Examiner).

Tian

Tian et al. (Reprod. Bio. & Endocrin., I(98): 1-7 (2003)) is cited for the proposition that, although somatic cells have varying cloning competence, and that specific cell types have been successful in producing cloned animals, "[a] clear consensus... has not been reached as to the superior somatic cell type for nuclear transfer." Again, there is no requirement in the U.S. patent law that one only describe and claim "superior" embodiments.

Tian also notes that "This is due in part to the fact that different laboratories employ diverse procedures; and cell culture, nuclear transfer, and micro manipulation all require critical technical skills." (pg. 3 immediately following the quote provided by the Examiner). She also observes that "Many somatic cell types, including mammary epithelial cells, ovarian cumulus cells, fibroblast cells from skin and internal organs, various internal organ calls, Sertolie cells, macrophages and blood leukocytes have been successfully utilized for nuclear transfer." (pg. 3)

Li

The Examiner further rejects the Applicants' arguments, as supported by the Ayares Declaration, that somatic cell nuclear transfer is simply a function of how many nuclear transfer units are implanted, citing Li et al. (Reprod. Bio. & Endocrin., I(84)1-6 (2003). Li is another reference that focuses on aspects of the inefficiency of the NT process as a means to achieve an

improvement. As stated above, enablement is not negated simply because a claimed method is inefficient, i.e., it must be repeated numerous times to achieve success. The Examiner points out that Li states that "Most cloned animals... fail to develop to term, and some of the surviving animals have shown abnormalities." That is not news in the nuclear transfer field, as expressed by Dr. Piedrahita, who states that people working in the field of SCNT live with low efficiency results and expect them in the area of nuclear transfer and cloning. Li also stated, however, that "Regardless of the inefficiencies of this process currently, morphologically normal living animals have been produced in 10 species..." (pg. 2), and that "Our data....provide evidence that nuclear transfer, despite multiple disorders, can result in physiologically normal, fertile animals." (pg. 2) .

McEvoy

McEvoy et al. (Reprod. Supp., 61: 167-182) and McEvoy et al., (Reproduction, 122: 507-508 (2001) have been cited by the Examiner as teaching that faulty or epigenetic reprogramming of the nuclear donor nucleus is responsible for the low efficiency and abnormal development said to be associated with cloning.

McEvoy concludes his Reproduction article with the following summary of his views:

> However, it is possible that we will only capitalize fully on the ever more sophisticated nuclear transfer and gene targeting technologies when unspectacular refinements to in vitro culture systems finally establish an environment that is hazard-free and that avoids perturbing the early regulation of mammalian development. Having already demonstrated what is possible, scientists must now realize that application of recent and remarkable research advances for the benefit of animal and human health will hereafter depend on minimizing, and preferably eliminating adverse consequences arising from in vitro manipulation of animal cells and embryos.

As with the other articles, McEvoy is focused on improving the efficiency of processes that have been shown to work.

In re Wands

The Examiner has cited to the Wands factors as supporting the rejection of the present claims. On the contrary, the fact pattern and binding decision of the Court of Appeals for the Federal Circuit in *In re Wands*, copy attached, strongly supports the patentability of the present claims.

In *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), the issue on appeal was whether the Board of Patent Appeals and Interferences erred in rejecting all remaining claims in a patent application

covering immunoassay methods for the detection of hepatitis B surface antigen (HGsAg) using high affinity monoclonal IgM antibodies. The rejection was based on the PTO's position that the production of the monoclonal antibodies was unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

On appeal, Wands argued that the specification fully enabled the claimed invention because the monoclonal antibodies needed to perform the immunoassay could be made from starting materials using methods well known in the art and that the applications of these methods to make the desired monoclonal antibody required only routine screening which did not amount to undue experimentation. The Board conceded that the methods used to prepare hybridomas and to screen them were either well known in the art or adequately disclosed in the specification, but noted that only 4 of 143 hybridomas, or 2.8% , were proven to produce the monoclonals that fell within the claims, and that antibodies that were proved to be high affinity IgM came from only 2 of 10 fusion experiments. Thus, the Board concluded that the methods were not predictable or reproducible, and that the low rate of demonstrated success established that a person skilled in the art would have to engage in undue experimentation to make the antibodies that fell within the claims. The CAFC reversed this decision of the PTO and the Board.

Citing *In re Forman*, 230 USPQ 546 (Bd.Pat.App. & Int. 1986), the *Wands* court held that undue experimentation is determined by a standard of reasonableness which can be assessed by examining eight factors: (1) quantity of experimentation necessary (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Reviewing the facts of the case, the *Wands* court found that that even if the 2.8% success rate was accepted, the court would not be required to reach a conclusion of undue experimentation. Rather, the court held, such a determination must be made in view of the circumstances of each case and cannot be made "solely by reference to a particular numerical cutoff." 858 F.2d at 738. Applying the factors enumerated in *In re Forman*, the court found that (i) the Wands' disclosure provided considerable direction and guidance on how to practice their invention and presented working examples; (ii) there was a high level of skill in the art at the time the application was filed; (iii) all of the methods needed to practice the invention were well known; and (iv) the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with the desire characteristics. Neither

party presented any evidence as to how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. The *Wands* court found that in the monoclonal antibody art, an "experiment" is not simply the screening of a single hybridoma, but rather the entire attempt to make a monoclonal antibody against a particular antigen, i.e., the process which entails immunization, fusion, cloning and screening the antibodies produced by the hybridomas for the desired characteristics.

The present fact pattern is strongly analogous to the fact pattern in Wands, in which the CAFC overturned a PTO decision of nonenablement. In the present case, (i) both the specification and published literature as of the priority date taught how to routinely carry out the somatic cell nuclear transfer process; (ii) as described by Dr. Piedrahita in his declaration, the researchers in this areas at that time were highly skilled and highly educated, the scientists had a Ph.D. degree and significant work experience in sophisticated laboratory molecular biology techniques and were considered among the "elite" of the animal veterinary research profession; (iii) all of the methods needed to practice the invention were well known; and (iv) the nature of nuclear transfer technology is that it involves the routine preparation and implantation of cloned embryos to determine which ones will mature to viability.

In the present case, as in *Wands*, it is also important to define the experiment. In transgenic animal cloning, the experiment is the entire attempt to make a transgenic animal, i.e., nuclear transfer, embryo activation, gestation to produce a successful clone. The nature of transgenic animal cloning involves multiple embryo transfers to produce a live birth.

It is also significant in the present case to note the quantity and quality of "experimentation" required to achieve a successful transgenic animal clone. In *Johns Hopkins University v. Cellpro, Inc.*, Johns Hopkins obtained patents on purified cell suspension of stem cells and monoclonal antibodies useful in producing such suspensions. 152 F.3d 1342 (Fed. Cir. 1998). One of these patents, the '204 patent, claimed the genus of antibodies which bind to a claimed antigen. The patent disclosed a method of producing one specific antibody, the anti-My-10 antibody, and Cellpro argued that the disclosure was insufficient to enable one of ordinary skill in the art to make and use the broader genus of claimed antibodies. Cellpro argued that one of ordinary skill in the art could only produce other antibodies in the genus with undue experimentation.

The experimentation required to produce other antibodies was repetition of the same process using different starting materials.

In finding that the patent was enabling, the court emphasized the test for undue experimentation. "The test for undue experimentation is not merely qualitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." *Id.* at 1361. Further, "[t]he enablement requirement is met if the description enables any mode of making and using the invention." *Id.*

The *Cellpro* patent adequately enabled the manufacture of one particular antigen, and repetition of the same process could allow the manufacture of other antigens in the claimed genus. The repetition required was not indicative of any shortcoming in the '204 patent but served as an indication of the state of the art at the relevant period. The Kohler/Milstein technique was "not foolproof" and "success with this technique commonly required repetition." *Id.* at 1360. The court held that "[t]his lack of certainty was thus not attributable to a failure of disclosure in the '204 patent" and does "not constitute undue experimentation." *Id.*

As in *Cellpro*, it is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. Application *of Angstadt*, 537 F.2d 498 (CCPA 1976). *See also Amgen, Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1336 (Fed. Cir. 2003) (holding that a single example was sufficient to support a broad claim where the court found that "any gaps between the disclosures and the claim breadth could be easily bridged," citing expert testimony that one of ordinary skill in the art would have understood the claim was not to be limited to the specific types of cells that were used in the example, that other vertebrate cells, mammalian cells, could have been used).

Thus, Applicants respectfully request withdrawal of the enablement rejection, and specifically as it relates to the enablement of any somatic cell to produce a transgenic mammal, as in the presently pending claims.

(ii) Homologous Recombination

The Examiner has also rejected claims 62-66, 70-73, 75-90, 98-127 and 131-133 as failing to comply with the enablement requirement because the specification fails to provide guidance with regard to how to select cells that have incorporated a particular homologous recombination event if the cells do not have a high proliferative potential. In his Declaration submitted with the 7/25/05 response to Office Action, Dr. Ayares confirmed that it was feasible

as of the priority date to obtain and screen for homologous recombination in cell types that do not have a high proliferative potential using the PCR techniques published by Zimmer and Gruss in 1989 and/or the FACS technique published by Jasin in 1990 (see Paragraphs 25-27 of Ayares Declaration). The Examiner responded that the PCR-based and FACS-based techniques described by Zimmer & Gruss and Jasin et al. are inapplicable because they apply to ES cells and non-primary somatic cells, respectively, instead of somatic cells. On the contrary, PCR and FACS-based techniques are not cell dependent.

Therefore, as early as 1989, several methods, including PCR-based and FACS-based techniques, were known to those skilled in the art, which could be used to detect targeted integration events after homologous recombination within 3-5 days. These methods allowed one to identify targeted clones, in a variety of cell types, without prolonged in vitro growth and expansion. It is clearly not a pre-requisite that cells to be used for homologous recombination and subsequent nuclear transfer must have high or even moderate proliferative potential. As described by Dr. Ayares, the use of Fluorescent Activated Cell Sorting (FACS) to rapidly detect homologous recombination events in transfected cells has facilitated genetic targeting in all cell types. The Jasin paper (Genes & Development (1990) 4: 132-166) was a fundamental publication that established the importance of this strategy of selection for gene targeting. The Jasin paper reported a 700-fold enrichment for homologous versus nonhomologous integration events by using FACS to select the targeted cells.

Dr. Piedrahita confirms the statement of Dr. Ayares with regard to homologous recombination, with the observation that a cell need not be highly proliferative, or even moderately proliferative, to undergo targeting by homologous recombination. Rather, homologous recombination requires only that a cell proliferate, regardless of rate. The technique of homologous recombination is described in the standard textbook "Gene Targeting: A Practical Approach. Alexandra L. Joyner, ed. Oxford University Press (1993).

Dr. Piedrahita agrees with Dr Ayares that it was well described in 1999 to obtain and screen for homologous recombination events using PCR and FACS-based screening regardless of whether the genetically modified cells had high proliferative potential. He notes that these methods permit a researcher to detected targeted integration events without prolonged in vitro growth and expansion, and that the methods are independent of what kind of cell is transfected. Dr. Piedrahita also confirms that it was irrelevant that the Zimmer and Gruss paper mentioned in Paragraph 26 of Dr. Ayares' declaration focused on ES cells or that the Jasin paper mentioned in

Paragraph 27 of the Ayares Declaration focused on cultured COS-1 cells. The techniques, PCR and FACS-based screening, are equally applicable to all cells.

(iii) Recipient Cells

The Examiner further rejected claims 62-66, 70-73, 75-90, 98-127 and 131-133 on the basis that particular oocytes (MMI, MII and telophase) have been found to be enabled by the prior art, but the claims are broader than this, reciting any oocyte. The Examiner also objects to the claims because they do not recite that the recipient oocyte/two-celled embryo or zygote is enucleate.

The Applicants have responded to this rejection by amending the claims to clarify that the oocyte, two cell embryo or zygote is capable of producing a viable nuclear transfer unit. This amendment addresses the Examiner's concerns about the cell cycle of the recipient, as it requires that the oocyte, two cell embryo or zygote be capable of receiving the donor genetic material and creating a viable nuclear transfer unit.

Applicants have not amended the claims to specify that the recipient cell needs to be enucleate at the time the nuclear genome of the somatic cell is transferred because the recipient cell does not need to be enucleate. Rather, the reconstructed embryo can be enucleated to restore the proper chromosomal complement, as known to those skilled in the art.

(iv) Species/ Genus

In response to the Examiner's concerns about whether the surrogate mother can carry the embryo to maturation, Applicants have amended the claims to confirm that the surrogate mother is a "suitable host, " in other words, that it is able to successfully carry the embryo to maturity, inter alia, to term.

(v) Abundant Expression

The Examiner further rejected the pending claims as failing to comply with the enablement requirement on the basis that there is no guidance as to what locus, other than the exemplified collagen locus, would provide the claimed 1:100 gene targeted cell: randomly targeted cell clone ratio. The Applicants have cancelled Claim 67 to satisfy the objection.

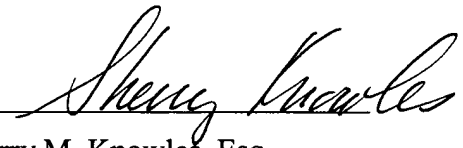
(vi) Genotype/ Phenotype

The Examiner has further rejected claims 62-66, 70-73, 75-90, 98-127 and 131-133 as failing to comply with the enablement requirement on the basis that without a particular phenotype, there is no enabled use for a particular transgenic animal. In response, the Applicants note that while transgenic animals may not at all times display a genetic changes, these animals are genotypically altered and thus are statutory subject matter as a material altered by man. The animals have an important use in breeding.

It is respectfully submitted that this application is now in condition for allowance. If the Examiner considers, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

KING & SPALDING LLP

By 

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Date: April 21, 2006